March 21, 2005 FDA Public Hearing on Reporting of Adverse Events (AEs) to Institutional Review Boards (IRBs)

Points for Consideration from PhRMA

Presented on behalf of PhRMA by

Jean-Louis Saillot, MD

Schering-Plough Research Institute

Member of PhRMA's Clinical Research and Pharmacovigilance & Epidemiology Technical Groups

Introduction & Background

- The issues with the current practice of sending large numbers of individual case reports are recognized by PhRMA companies, and PhRMA praises the FDA for organizing a dialogue around these issues.
- Drivers for the current situation
  - The current regulatory framework and guidance documents, including FDA IND regulations and ICH E6 guidance on Good Clinical Practice drive the expedited submission of clinical trial adverse events cases reports which are serious, unexpected and at least possibly related to the product(s) under investigation.
  - These reports are to be submitted to Regulatory Authorities as well as Investigators involved in the study, in most situations within 15 calendar days from the receipt of the information by the Sponsor
  - It is in turn the responsibility of the investigators to inform their IRB(s). Sponsors routinely monitor that investigators fulfill their responsibilities.

Background (cont'd)

- Changes to the current framework are currently ongoing
  - Example of the European Clinical Trial Directive
    - Expedited reports (Suspected Unexpected Serious Adverse Reactions or SUSARs) are to be submitted by Sponsors to both Investigators and Ethics Committees (in addition to their submission by the Sponsor to Regulatory Health Authorities)
    - Introduction of new reporting requirements
      - Quarterly line listings
      - Annual Safety Report
- Broad recognition of the issues associated with the current reporting process for individual cases reports
  - Example of the recent CIOMS VI working group recommendations

Recent CIOMS VI Report

- *The CIOMS VI Working Group recommends replacing the current practice of sending large numbers of individual case reports to investigators and ethics committees with a more reasonable approach to communicating important safety information to all who need to know. Such an approach would involve periodic and* ad hoc *communications to investigators and ethics committees that include an update of important safety information as well as the evolving benefit-risk profile.*

Points for Consideration (1)

- Main focus is on addressing FDA's question #3, but also provides elements which may be relevant to question # 2
  - Information provided to the IRBs should be complete, timely and meaningful
    - The current process ensures timeliness, but does not best address completeness or meaningfulness
  - Aggregate safety information should be provided at periodic intervals together with an evaluation of the evolving safety profile of the product under investigation

Points for Consideration (2)

- In addition to the aggregate safety information, ad hoc reports of meaningful safety information (e.g., information which has implication for the conduct of the trial) should be provided to investigators and IRBs, as these are received by Sponsors.
  - Only meaningful single reports would be communicated on an expedited basis (e.g., single events which due to their nature bring significant new safety information which has implication for the conduct of the trial)
  - Additional information which is meaningful, but not in the form of single reports (e.g., pre-clinical or clinical study results which bring significant new safety information and have implication for the conduct of the trial) would also qualify for ad-hoc, expedited reporting (consistent with current regulations)

Additional Important Elements for Consideration

- The difficulty to manage individual case reports is not impacting just IRBs, but also investigators
- Focus on providing only relevant reports on an expedited basis to sites, with periodic reporting of aggregate information together with an evaluation of the accumulating safety information will also provide investigators with better information to help them with their obligation of oversight of the trial at their sites
- Current expedited reporting to Regulatory Health Authorities would remain unchanged

Additional Important Elements for Consideration (cont'd)

- As FDA reevaluates the process of reporting safety information to IRBs, PhRMA urges the Agency to also evaluate the value of more meaningful reporting to investigators. In this respect the proposals outlined in the recently completed CIOMS VI report are considered extremely valuable.
- Preparation of Guidance within the ICH process is also planned to include the concepts of the CIOMS VI reports. PhRMA would also like to re-emphasize the value of the harmonization of reporting approaches across the sites involved in the research activities (including sites outside of the US).

Conclusions

- PhRMA companies recognize the issue identified by the IRB community and agree that the current system for notification of safety information to IRB can and should be improved.
- PhRMA recognizes that more meaningful information to the IRBs will help in their role to protect the public, thereby improving the overall Clinical Research process.
- PhRMA urges FDA to take the opportunity of this review to also address the issue of individual case reporting to investigators